

# Pulmonary reperfusion injury

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## ABSTRACT

Pulmonary reperfusion injury is a clinical syndrome with no single and recognized pathophysiologic mechanism. It is a major cause of morbidity and mortality following lung transplantation, cardiogenic shock, or cardiopulmonary bypass. The underlying mechanisms remain uncertain. Lung inflammatory injury induced by lipopolysaccharide, characterized by rapid sequestration of neutrophils in response to inflammatory chemokines and cytokines released in the lungs is an acceptable theory. Structural or functional impairment of surfactant has been noted in pulmonary reperfusion injury. The pathological changes may include bilateral pulmonary infiltrates, reduced lung compliance and worsening of gas exchange in the immediate posttransplant period. Recruitment maneuver and high positive end-expiratory pressure can relieve postoperative respiratory failure, especially in the patient with reperfusion pulmonary edema after pulmonary thromboendarterectomy. Pharmaceutical agents, including inhaled nitric oxide, soluble complement receptor type 1, prostaglandin E1 and exogenous surfactant, attenuate pulmonary reperfusion injury through distinct mechanisms. Extracorporeal membrane oxygenation and Novalung are temporary assistance in bridging to lung transplantation, stabilization of hemodynamics during transplantation and treatment of severe lung dysfunction and primary graft failure. Modulation of heme oxygenase-1 expression, ischemic conditioning and gene therapy are future directions for pulmonary reperfusion injury management.

**Key words:** cardiopulmonary bypass, pulmonary hypertension, respiratory insufficiency

## INTRODUCTION

Pulmonary reperfusion injury is a common clinical problem secondary to severe shock, cardiopulmonary bypass (CPB) and lung transplantation, etc. (1) It is a major cause of morbidity, predominantly primary graft dysfunction (PGD) and mortality following lung transplantation. (2,3) Ischemia and reperfusion are two distinct events due to the fact that the resultant pathological changes of the lungs are different. Reperfusion injury is a worsening lesion developing from the ischemia injury. (4) Pulmonary reperfusion injury is characterized by non-specific alveolar damage, lung edema and hypoxemia occurring within 72 hours. (5) After CPB, lung disturbances, including increased lung permeability and pulmonary vascular resistance, as well as lung surfactant changes, develop. (6)

## MECHANISMS

Mechanisms of pulmonary reperfusion injury have been extensively studied. Complete and prolonged lung anoxia for up to several hours is unavoidable during lung transplantation. (7) Lung injury often occurs within the first few seconds to hours after reperfusion, as evidenced by experiments in different models. (8) However, the exact pathogenesis of pulmonary reperfusion injury remains uncertain. Lung inflammatory injury induced by lipopolysaccharide characterized by rapid sequestration of neutrophils in response to inflammatory chemokines and cytokines released in the lungs is an acceptable theory. (9) Pulmonary reperfusion injury after lung transplantation is also mediated by oxidative stress-dependent mechanisms involving nicotinamide adenine dinucleotide phosphate oxidase and by apoptosis, (10) and the central role of nuclear factor-

κB in the induction of lung inflammatory injury is now emerging. (11) In lung tissue biopsies obtained from 20 consecutive human lungs for transplantation, apoptotic cells increased in number after graft reperfusion in a time-dependent manner. (12) In a rat lung transplant model, cell viability determinations revealed that lung function decreased significantly with increasing preservation time and that the necrotic cell percentage was inversely correlated with posttransplant graft function. (2) The peak apoptotic rate of pneumocytes occurred 2 hours after reperfusion in rats with single lung transplantation. (13)

Structural or functional impairment of surfactant has been noted in pulmonary reperfusion injury. (14) In contrast, the surfactant changes in adult respiratory distress syndrome patients were considered to be caused by lung dysfunction. (9) Nuclear factor-κB is a rapid response transcription factor that activates genes responsible for the mediators of inflammation. In a porcine transplantation model, nuclear factor-κB played a central role in triggering the pathways for lung inflammatory injury. Activation of nuclear factor-κB occurred 30 minutes and 1 hour after transplantation and fell to near baseline levels after 4 hours. Pyrrolidine dithiocarbamate, a potent inhibitor of nuclear factor-κB, given to the lung graft during organ preservation (40 mmol/L) effectively inhibited nuclear factor-κB activation and significantly improved lung function. (11) Heat shock protein 70 has been shown to protect against lung injury. (15) In rabbits with depletion of neutrophils, pulmonary ischemia-reperfusion injury occurred when the ischemic lungs were deflated but did not occur when the ischemic lungs were inflated. (1) Oxidative stress and apoptosis may also play an important role in the development of pulmonary reperfusion injury. (10) Animal experiments revealed that CPB caused a threefold increase in the exter-

nal pulmonary protein leak index, and slightly increased extravascular lung water. Moderately elevated left atrial pressure may increase lung water >50% after CPB compared with control, but peak endotoxin and minimum total complement CH50 levels did not. (16) An early phase of endotoxin release due to vasoconstriction could be noted during CPB. The endotoxin concentrations at CPB termination relied on early vasoconstriction, duration of aortic crossclamping and hypo-oncotic hemodilution. (17) However, a prospective clinical study revealed that off-pump coronary artery bypass does not confer major protection from postoperative pulmonary dysfunction in comparison to conventional coronary artery bypass grafting under CPB. (18) It hinted that CPB might not be a direct causative etiology responsible for postoperative pulmonary dysfunction. Nevertheless, normothermic CPB may reduce intrapulmonary shunt function and alveolar-arterial oxygen and carbon dioxide gradients and therefore may preserve lung function. (19)

Prolonged pulmonary ischemia and subsequent reperfusion injury occur during procedures such as pulmonary endarterectomy, hypothermic circulatory arrest and lung transplantation. Extrapulmonary ischemia-reperfusion can also contribute to lung injury. (20) Inflammatory cytokines including interleukin-8 (21) or matrix metalloproteinase 9 (22) may be upregulated secondary to donor lung injury or surgical trauma. The inflammatory responses also link to interleukin-1 $\beta$ , which induces the action of the cyclooxygenase (COX) and the expression of the inductive nitric oxide synthase (iNOS). (23) It also increases the expression of other cytokines such as interleukin-6 as well TNF- $\alpha$ . (23,24)

Pulmonary thromboendarterectomy is a potentially curative procedure in chronically thromboembolic pulmonary artery hypertension. The early mortality rate in 54 patients between 1989 and 1992 was 22.2% (12/54) and currently below 7%. (25) Reperfusion pulmonary edema can be a result of the development of hypoxemia and radiological infiltrates in areas of reperfused endarterectomy. (26) Levinson et al. (27) reported 22 patients had postoperative reperfusion pulmonary edema, which developed within 72 hours following pulmonary thromboendarterectomy. **Diagnosis**

Bilateral pulmonary infiltrates, reduced lung compliance and worsening of gas exchange in the immediate posttransplant period are helpful to the diagnosis. (28) Medical imaging including chest radiogra-

phy and chest computed tomography may show characteristic pulmonary changes of graft capillary leakage and infiltrates, pleural effusions or lung edema on chest radiography and chest computed tomography. (29)

## PREVENTION

Pulmonary preservation for transplantation is associated with ischemia-reperfusion injury resulting in endothelial cell and surfactant dysfunction. (30) The preservation method is pulmonary artery perfusion with a preservation solution at 4°C, which may cool the tissue evenly and remove blood from the pulmonary vascular bed, preventing thrombosis and attenuating cellular injury caused by macrophages and neutrophils. (31) In a rat model of double lung transplantation, a comparative study of lung preservation solutions revealed low potassium dextran provided superior graft function to Euro-Collins, low potassium Euro-Collins and University of Wisconsin solution after extended ischemia. (32) In a porcine lung transplantation model, after 24 hours of cold ischemia, low potassium dextran or Celsior solution provided safe pulmonary preservation, while surfactant activity was affected to the same extent. Celsior solution showed slightly superior endothelial preservation. (30) The largest cohort study of adult lung transplantation survival revealed that low potassium dextran was superior to University of Wisconsin solution, the latter increasing the risk of 1-year mortality in high-risk lung transplant recipients. (33) Haverich et al. (34) found that lungs flushed with a high perfusate volume given at a high flow rate (60 mL/kg given in 4 minute) resulted in significantly better pulmonary cooling and better lung function after reperfusion in comparison to low perfusate volume given at a low flow rate (20 mL/kg given in 6 minute) with a low perfusate volume given at a high flow rate (20 mL/kg given in 1.3 minute). Alternative studies demonstrated that lung function was significantly better after reperfusion if the lungs were initially flushed with a temperature of 15–20°C instead of  $\leq 10^\circ\text{C}$  as observed in small animals and surface cooling of the inflated lungs. (35) Steen et al. (36) recommended that if the temperature of the flush solution was kept at room temperature, the lungs should be kept collapsed during cold storage to reduce core temperature quicker by avoiding the insulating effect of air.

## TREATMENT

### *Recruitment maneuver*

Recruitment maneuver and high positive end-expiratory pressure can relieve postoperative respiratory failure, especially in the patient with reperfusion pulmonary edema after pulmonary thromboendarterectomy for chronic pulmonary thromboembolism. With recruitment maneuvers: positive end-expiratory pressure, 30 cmH<sub>2</sub>O, peak inspiratory pressure, 42 cmH<sub>2</sub>O and respiratory rate, 15 breaths/min for 1 min with a high positive end-expiratory pressure of 15 cmH<sub>2</sub>O, the reperfusion pulmonary edema can be gradually relieved, followed by improvement of oxygenation and pulmonary hypertension. (37)

## PHARMACOLOGICAL THERAPY

### *1. Inhaled nitric oxide (iNO)*

iNO can mediate pulmonary vasodilation and improve pulmonary function in patients with lung injury, treatment of lung allograft recipients with iNO may ameliorate ischemia-reperfusion injury, thereby improving perioperative pulmonary function and diminishing ventilatory support requirements. (38) iNO suppressed pulmonary hypertension after reperfusion, and might enhance suppression of oxygen free radicals and therefore may be therapeutically useful after lung transplantation. (39) The administration of iNO during lung transplantation was proposed as a possible therapeutic treatment to prevent or attenuate PGD. There was evidence that iNO in patients with PGD might improve oxygenation and reduce pulmonary hypertension without altering systemic vascular resistance. This suggested that iNO could prevent the need for extracorporeal membrane oxygenation during the hypoxic phase of primary graft failure. (40) Experiments proved that iNO attenuated apoptosis in ischemia-reperfusion injury of the rabbit lung. The number of apoptotic cells was remarkably reduced in the iNO group than in the control after 120-minutes of reperfusion (1.76% vs. 2.87%,  $p < 0.01$ ). (41) Clinical studies of lung transplant patients showed iNO may improve hemodynamic parameters. (42)

### *2. Prostaglandins*

Prostaglandin E1 has been demonstrated to reduce ischemia-reperfusion injury following lung transplantation. (43) In a rat single lung transplant model, prostaglandin E1 does not decrease the amount of

apoptosis after reperfusion and does not significantly upregulate B-cell lymphoma 2. Administration of prostaglandin E1 during the reperfusion period reduces ischemia-reperfusion injury through a mechanism mediated by a shift between pro- and anti-inflammatory cytokine releases. (43) Experiments of reperfusion on ischemic lung injury in an in situ rabbit model showed that prostaglandin E1 may exert a direct cytoprotective effect other than by its vasodilating properties or the known effects of prostaglandin E1 on platelets, neutrophils, or tumor necrosis factor suppression. (44)

### 3. Soluble complement receptor type 1 (sCR1)

Soluble complement receptor type 1 (sCR1) is a powerful inhibitor of complement activation. sCR1 protects the myocardium and lungs from some of the deleterious effects of CPB. The significantly higher arterial partial tension of oxygen after CPB in the sCR1 animals suggests that sCR1 protects lung function. Gillinov et al. (45) reported, in young pigs, that after CPB, pulmonary vascular resistance increased by 338% in control but only by 147% in sCR1-treated animals. This was in line with the results reported by Chai et al. (46) from neonatal pigs, i.e., after CPB pulmonary vascular resistance increased by 350% and 120% in the control and sCR1 groups, respectively.

### 4. Platelet-activating factor antagonists

Platelet activating factor is an inflammatory mediator produced by a variety of cells in response to inflammatory and immune stimuli, and is implicated in a wide range of pathological conditions including ischemia-reperfusion injury after lung transplantation. (47) Platelet-activating factor antagonists reduce pulmonary reperfusion injury by inhibition of neutrophil accumulation, eosinophilic inflammation and chemotaxis. (48) Platelet activating factor antagonists given before organ reperfusion significantly improve lung function after lung transplantation. (49)

### 5. Surfactant

Surfactant dysfunction occurs during ischemia-reperfusion injury. Exogenous surfactant therapy improves lung function by stabilizing and enhancing the ac-

tive endogenous surfactant, (50) and decreasing the development of intraalveolar edema and atelectasis, but worsening the peribronchovascular edema. (51) Delivery methods of exogenous surfactant remain challenging, but bronchoscopic instillation to aerosolized surfactant is preferred. (7)

## EXTRACORPOREAL MEMBRANE OXYGENATION

Indications for extracorporeal membrane oxygenation use in lung transplantation are temporary assistance as a bridge to transplantation, stabilization of hemodynamics during transplantation, and treatment of severe lung dysfunction and PGD after transplantation. However, patient survival was significantly reduced with the use of extracorporeal membrane oxygenation, although it can provide acceptable support for PDG after lung transplantation. (52-54)

## NOVALUNG

Novalung is an evolving support system to bridge patients with idiopathic pulmonary hypertension to lung transplantation with a modified surgical technique for left pulmonary artery-to-left atrium bypass. With the application of Novalung, pulmonary artery systolic pressures can be decreased and the patient's oxygenation improved. (55)

## FUTURE DIRECTIONS

Endogenous expression of heme oxygenase-1 represents a transcriptional response to oxidative stress. Heme oxygenase-1 provides potent cytoprotective effects. Enhanced endogenous heme oxygenase-1 and its downstream mediators protect against the sequel of ischemia-reperfusion injury. (56) In order to obtain biological adaptation, tissues are exposed to a brief insult, by which tolerance of organs to a subsequent reperfusion injury is anticipated, and this process is termed as preconditioning. (57) Ischemic preconditioning is usually achieved by brief periods of ischemia and reperfusion before a

prolonged period of ischemia and it can reduce the ischemic-reperfusion injury in solid organs. (58) Nowadays, preconditioning has been expanded to hyperthermic preconditioning by increased temperature and chemical preconditioning by administration of pharmacologic agents. (57) Ischemic preconditioning of guinea pig lungs mounted on a modified Langendorff perfusion resulted in reduced malondialdehyde and glutathione levels and less elevated pulmonary artery pressure. (59) The mechanism seemed to be at least partly by stimulating autophagy. (59) Recent research results also revealed that ischemic postconditioning attenuates lung reperfusion injury and reduces systemic proinflammatory cytokine release via heme oxygenase-1. (60) Gene therapy, such as transfection of the gene coding for transforming growth factor  $\beta$ 1 and interleukin-10, were proved to reduce ischemia-reperfusion injury and improve lung function in a rat single lung transplant model. (61,62) It has been noted that in rat lung transplantation models, a minimal 12-hour transtracheal administration of interleukin-10 to the donor lungs may improve post-transplant lung functions. (63) Human lung protection by gene therapy will come to true soon.

## CONCLUSIONS

Pulmonary reperfusion injury is a major cause of PGD and mortality following lung transplantation, cardiogenic shock or CPB. The underlying mechanisms remain uncertain. Lung inflammatory injury induced by lipopolysaccharide, characterized by rapid sequestration of neutrophils in response to inflammatory chemokines and cytokines released in the lungs is an acceptable theory. The management strategies for pulmonary reperfusion injury are similar to those for adult respiratory distress syndrome with stresses on pharmaceutical agents including inhaled nitric oxygen, prostaglandin E1 and surfactant replacement therapy for the former, and on ventilation treatment for worsening respiratory mechanics for the latter.

## REFERENCES

1. Sakuma T, Takahashi K, Ohya N, Kajikawa O, Martin TR, Albertine KH, et al. Ischemia-reperfusion lung injury in rabbits: mechanisms of injury and protection. *Am J Physiol* 1999;276(1 Pt 1):L137-45.
2. Fischer S, Maclean AA, Liu M, Cardella JA, Slutsky AS, Suga M, et al. Dynamic changes in apoptotic and necrotic cell death correlate

with severity of ischemia-reperfusion injury in lung transplantation. *Am J Respir Crit Care Med* 2000;162(5):1932-9.

3. Okada Y, Kondo T. Preservation solution for lung transplantation. *Gen Thorac Cardiovasc Surg* 2009;57(12):635-9.
4. Fadel E, Mazmanian GM, Chapelier A, Baudet B, Detruit H, de Montpreville V, et al. Lung reperfusion injury after chronic or acute unilateral pulmonary artery occlusion. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1294-300.
5. de Perrot M, Liu M, Waddell TK, Keshavjee S. Ischemia-reperfusion-induced lung injury. *Am J Respir Crit Care Med* 2003;167(4):490-511.
6. Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. *Chest* 2002;121(4):1269-77.
7. den Hengst WA, Gielis JF, Lin JY, Van Schil PE, De Windt LJ, Moens AL. Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process. *Am J Physiol Heart Circ Physiol* 2010;299(5):H1283-99.
8. Matot I, Einav S, Weiniger CF, Pearl RG, Abramovitch R, Joshi BV, et al. Lung injury after in vivo reperfusion: outcome at 27 hours after reperfusion. *Anesthesiology* 2008;109(2):269-78.
9. Della Rocca G, Pierconti F, Costa MG, Coccia C, Pompei L, Rocco M, et al. Severe reperfusion lung injury after double lung transplantation. *Crit Care* 2002;6(3):240-4.
10. Chen W, Zheng G, Yang S, Ping W, Fu X, Zhang N, et al. CYP2J2 and EETs protect against oxidative stress and apoptosis in vivo and in vitro following lung ischemia/reperfusion. *Cell Physiol Biochem* 2014;33(6):1663-80.
11. Ross SD, Kron IL, Gangemi JJ, Shockey KS, Stoler M, Kern JA, et al. Attenuation of lung reperfusion injury after transplantation using an inhibitor of nuclear factor- $\kappa$ B. *Am J Physiol Lung Cell Mol Physiol* 2000;279(3):L528-36.
12. Fischer S, Cassivi SD, Xavier AM, Cardella JA, Cutz E, Edwards V, et al. Cell death in human lung transplantation: apoptosis induction in human lungs during ischemia and after transplantation. *Ann Surg* 2000;231(3):424-31.
13. Stammberger U, Gaspert A, Hillinger S, Vogt P, Odermatt B, Weder W, et al. Apoptosis induced by ischemia and reperfusion in experimental lung transplantation. *Ann Thorac Surg* 2000;69(5):1532-6.
14. Ochs M, Nenadic I, Fehrenbach A, Albes JM, Wahlers T, Richter J, et al. Ultrastructural alterations in intraalveolar surfactant subtypes after experimental ischemia and reperfusion. *Am J Respir Crit Care Med* 1999;160(2):718-24.
15. Long SM, Laubach VE, Tribble CG, Kaza AK, Fiser SM, Cassada DC, et al. Pyrrolidine dithiocarbamate reduces lung reperfusion injury. *J Surg Res* 2003;112(1):12-8.
16. Dauber IM, Parsons PE, Welsh CH, Giclas PC, Whitman GJ, Wheeler GS, et al. Peripheral bypass-induced pulmonary and coronary vascular injury. Association with increased levels of tumor necrosis factor. *Circulation* 1993;88(2):726-35.
17. Jansen PG, Te Velthuis H, Oudemans-Van Straaten HM, Bulder ER, Van Deventer SJ, et al. Perfusion-related factors of endotoxin release during cardiopulmonary bypass. *Eur J Cardiothorac Surg* 1994;8(3):125-9.
18. Montes FR, Maldonado JD, Paez S, Ariza F. Off-pump versus on-pump coronary artery bypass surgery and postoperative pulmonary dysfunction. *J Cardiothorac Vasc Anesth* 2004;18(6):698-703.
19. Ranucci M, Soro G, Frigiola A, Menicanti L, Ditta A, Candido G, et al. Normothermic perfusion and lung function after cardiopulmonary bypass: effects in pulmonary risk patients. *Perfusion* 1997;12(5):309-15.
20. Stephens RS, Shah AS, Whitman GJ. Lung injury and acute respiratory distress syndrome after cardiac surgery. *Ann Thorac Surg* 2013;95(3):1122-9.
21. De Perrot M, Sekine Y, Fischer S, Waddell TK, McRae K, Liu M, et al. Interleukin-8 release during early reperfusion predicts graft function in human lung transplantation. *Am J Respir Crit Care Med* 2002;165(2):211-5.
22. Yano M, Omoto Y, Yamakawa Y, Nakashima Y, Kiriya M, Saito Y, et al. Increased matrix metalloproteinase 9 activity and mRNA expression in lung ischemia-reperfusion injury. *J Heart Lung Transplant* 2001;20(6):679-86.
23. Delbin MA, Antunes E, Zanesco A. Role of exercise training on pulmonary ischemia/reperfusion and inflammatory response. *Rev Bras Cir Cardiovasc* 2009;24(4):552-61.
24. Santos CH, Aydos RD, Nogueira Neto E, Mijji LN, Cassino PC, Alves II, et al. Evaluation of pulmonary reperfusion injury in rats undergoing mesenteric ischemia and reperfusion and protective effect of postconditioning on this process. *Rev Bras Cir Cardiovasc* 2015;30(5):533-7.
25. Kramm T, Mayer E, Dahm M, Guth S, Menzel T, Pitton M, et al. Long-term results after thromboendarterectomy for chronic pulmonary embolism. *Eur J Cardiothorac Surg* 1999;15(5):579-83; discussion 583-4.
26. Kerr KM, Auger WR, Marsh JJ, Comito RM, Fedullo RL, Smits GJ, et al. The use of cylexin (CY-1503) in prevention of reperfusion lung injury in patients undergoing pulmonary thromboendarterectomy. *Am J Respir Crit Care Med* 2000;162(1):14-20.
27. Levinson RM, Shure D, Moser KM. Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. *Am Rev Respir Dis* 1986;134(6):1241-5.
28. Zaas D, Palmer SM. Respiratory failure early after lung transplantation: now that we know the extent of the problem, what are the solutions? *Chest* 2003;123(1):14-6.
29. Struber M, Hirt SW, Cremer J, Harringer W, Haverich A. Surfactant replacement in reperfusion injury after clinical lung transplantation. *Intensive Care Med* 1999;25(8):862-4.
30. Sommer SP, Warnecke G, Hohlfeld JM, Gohrbandt B, Niedermeyer J, Kofidis T, et al. Pulmonary preservation with LPD and celsior solution in porcine lung transplantation after 24 h of cold ischemia. *Eur J Cardiothorac Surg* 2004;26(1):151-7.
31. Medeiros IL, Pego-Fernandes PM, Mariani AW, Fernandes FG, Unterpertinger FV, Canzian M, et al. Comparison of lung preservation solutions in human lungs using an ex vivo lung perfusion experimental model. *Clinics (Sao Paulo)* 2012;67(9):1101-6.
32. Hausen B, Beuke M, Schroeder F, Poets CF, Hewitt C, DelRossi AJ, et al. In vivo measurement of lung preservation solution efficacy: comparison of LPD, UW, EC and low K<sup>+</sup>-EC following short and extended ischemia. *Eur J Cardiothorac Surg* 1997;12(5):771-9; discussion 779-80.
33. Arnaoutakis GJ, Allen JG, Merlo CA, Baumgartner WA, Conte JV, Shah AS. Low potassium dextran is superior to University of Wisconsin solution in high-risk lung transplant recipients. *J Heart Lung Transplant* 2010;29(12):1380-7.



34. Haverich A, Aziz S, Scott WC, Jamieson SW, Shumway NE. Improved lung preservation using Euro-Collins solution for flush-perfusion. *Thorac Cardiovasc Surg* 1986;34(6):368-76.
35. Wang LS, Nakamoto K, Hsieh CM, Miyoshi S, Cooper JD. Influence of temperature of flushing solution on lung preservation. *Ann Thorac Surg* 1993;55(3):711-5.
36. Steen S, Kimblad PO, Sjöberg T, Lindberg L, Ingemansson R, Massa G. Safe lung preservation for twenty-four hours with Perfadex. *Ann Thorac Surg* 1994;57(2):450-7.
37. Tachibana K, Imanaka H, Miyano H, Takeuchi M, Kumon K, Ando M, et al. Recruitment maneuver and high PEEP in a patient with severe reperfusion pulmonary edema after pulmonary thromboendarterectomy. *Masui* 2003;52(1):52-7.
38. Meyer KC, Love RB, Zimmerman JJ. The therapeutic potential of nitric oxide in lung transplantation. *Chest* 1998;113(5):1360-71.
39. Fukahara K, Murakami A, Watanabe G, Kotoh K, Misaki T. Inhaled nitric oxide after lung ischemia reperfusion; effect on hemodynamics and oxygen free radical scavenger system. *Eur J Cardiothorac Surg* 1997;11(2):343-9.
40. Pasero D, Martin EL, Davi A, Mascia L, Rinaldi M, Ranieri VM. The effects of inhaled nitric oxide after lung transplantation. *Minerva Anestesiol* 2010;76(5):353-61.
41. Yamashita H, Akamine S, Sumida Y, Inoue M, Sawada T, Nagayasu T, et al. Inhaled nitric oxide attenuates apoptosis in ischemia-reperfusion injury of the rabbit lung. *Ann Thorac Surg* 2004;78(1):292-7.
42. Rea RS, Ansani NT, Seybert AL. Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother* 2005;39(5):913-7.
43. de Perrot M, Fischer S, Liu M, Jin R, Bai XH, Waddell TK, et al. Prostaglandin E1 protects lung transplants from ischemia-reperfusion injury: a shift from pro- to anti-inflammatory cytokines. *Transplantation* 2001;72(9):1505-12.
44. Matsuzaki Y, Waddell TK, Puskas JD, Hirai T, Nakajima S, Slutsky AS, et al. Amelioration of post-ischemic lung reperfusion injury by prostaglandin E1. *Am Rev Respir Dis* 1993;148(4 Pt 1):882-9.
45. Gillinov AM, DeValeria PA, Winkelstein JA, Wilson I, Curtis WE, Shaw D, et al. Complement inhibition with soluble complement receptor type 1 in cardiopulmonary bypass. *Ann Thorac Surg* 1993;55(3):619-24.
46. Chai PJ, Nassar R, Oakeley AE, Craig DM, Quick G Jr, Jaggars J, et al. Soluble complement receptor-1 protects heart, lung, and cardiac myofilament function from cardiopulmonary bypass damage. *Circulation* 2000;101(5):541-6.
47. Curtin ML. Current status of platelet-activating factor antagonists. *Expert Opin Ther Pat* 1998;8(6):703-711. doi:10.1517/13543776.8.6.703.
48. Kurihara K, Wardlaw AJ, Moqbel R, Kay AB. Inhibition of platelet-activating factor (PAF)-induced chemotaxis and PAF binding to human eosinophils and neutrophils by the specific ginkgolide-derived PAF antagonist, BN 52021. *J Allergy Clin Immunol* 1989;83(1):83-90.
49. Corcoran PC, Wang Y, Katz NM, St Louis JD, Foegh ML, Rajan SS, et al. Platelet activating factor antagonist enhances lung preservation. *J Surg Res* 1992;52(6):615-20.
50. Muhlfeld C, Becker L, Bussinger C, Vollroth M, Nagib R, Schaefer IM, et al. Exogenous surfactant in ischemia/reperfusion: effects on endogenous surfactant pools. *J Heart Lung Transplant* 2010;29(3):327-34.
51. Dreyer N, Muhlfeld C, Fehrenbach A, Pech T, von Berg S, Nagib R, et al. Exogenous surfactant application in a rat lung ischemia reperfusion injury model: effects on edema formation and alveolar type II cells. *Respir Res* 2008;9:5. doi: 10.1186/1465-9921-9-5.
52. Bittner HB, Lehmann S, Rastan A, Garbade J, Binner C, Mohr FW, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery. *Ann Thorac Surg* 2012;94(3):942-9; author reply 949-50.
53. Bermudez CA, Adusumilli PS, McCurry KR, Zaltonis D, Crespo MM, Pilewski JM, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: long-term survival. *Ann Thorac Surg* 2009;87(3):854-60.
54. Oto T, Rosenfeldt F, Rowland M, Pick A, Rabinov M, Prevolos A, et al. Extracorporeal membrane oxygenation after lung transplantation: evolving technique improves outcomes. *Ann Thorac Surg* 2004;78(4):1230-5.
55. Patil NP, Mohite PN, Reed A, Popov AF, Simon AR. Modified technique using Novalung as bridge to transplant in pulmonary hypertension. *Ann Thorac Surg* 2015;99(2):719-21.
56. Tsuchihashi S, Fondevila C, Kupiec-Weglinski JW. Heme oxygenase system in ischemia and reperfusion injury. *Ann Transplant* 2004;9(1):84-7.
57. Simon R. Post-conditioning and reperfusion injury in the treatment of stroke. *Dose Response* 2014;12(4):590-9.
58. Soncul H, Oz E, Kalaycioglu S. Role of ischemic preconditioning on ischemia-reperfusion injury of the lung. *Chest* 1999;115(6):1672-7.
59. Gao M, Liu D. Ischemic preconditioning may attenuate lung ischemia-reperfusion injury partly by stimulating autophagy. *J Formos Med Assoc* 2015;114(8):677-8.
60. Xu B, Gao X, Xu J, Lei S, Xia ZY, Xu Y, et al. Ischemic postconditioning attenuates lung reperfusion injury and reduces systemic proinflammatory cytokine release via heme oxygenase 1. *J Surg Res* 2011;166(2):e157-64.
61. Daddi N, Suda T, D'Ovidio F, Kanaan SA, Tagawa T, Grapperhaus K, et al. Recipient intramuscular cotransfection of naked plasmid transforming growth factor  $\beta$ 1 and interleukin 10 ameliorates lung graft ischemia-reperfusion injury. *J Thorac Cardiovasc Surg* 2002;124(2):259-69.
62. Fischer S, De Perrot M, Liu M, MacLean AA, Cardella JA, Imai Y, et al. Interleukin 10 gene transfection of donor lungs ameliorates posttransplant cell death by a switch from cellular necrosis to apoptosis. *J Thorac Cardiovasc Surg* 2003;126(4):1174-80.
63. de Perrot M, Fischer S, Liu M, Imai Y, Martins S, Sakiyama S, et al. Impact of human interleukin-10 on vector-induced inflammation and early graft function in rat lung transplantation. *Am J Respir Cell Mol Biol* 2003;28(5):616-25.